REMARKS

With this Amendment, Claims 3-5 and 12 have been amended, and new Claims 32 to 43 have been added. After entry of this Amendment, Claims 1-16, and 30-43 are pending in the instant Application.

Patent Application Publication U.S. 2002/0061539 A1

The Examiner's attention is drawn to a printing error that Applicants have discovered in patent application publication U.S. 2002/0061539 A1 that derives from the instant application. Pages 98 through 167 inclusive are duplicates of pages 28 through 97 inclusive, and have been printed in error. Thus, pages 98 through 167 inclusive should be deleted in their entirety as and when a patent issues from the instant application.

Applicants understand that the time within which it would be possible to request republication of the application, under 37 C.F.R. § 1.221(b), has expired and therefore are merely drawing the Examiner's attention to the error at this time. Applicants respectfully request that the Examiner brings this error to the attention of the publication division at such time as a notice of allowance is mailed.

Sequence listing

Applicants submit herewith a substitute sequence listing under 37 C.F.R. § 1.825. This sequence listing replaces the sequence listing mailed March 24, 2000 and corrected on April 26, 2000, and contains sequences newly labeled SEQ ID NOS. 52 – 60, each of which corresponds to a protein fragment presented in the Protein Data Bank (PDB) files found in Appendices 1–3 of the specification as filed.

As would be understood by one of skill in the art, a PDB file provides a sequence of amino acids in order of connectivity in one or more polypeptide chains. The format of a PDB file is well known in the art, and a description is available on the world wide web at http://www.rcsb.org/pdb/docs/format/pdbguide2.2/guide2.2_frame.html. This description is dated December 1996, and would have been available prior to the filing date of the instant application.

In particular, a PDB file contains the atomic coordinates, residue name, and sequence number of each resolved non-hydrogen atom in a crystal structure of a protein or protein

fragment. Where there is more than one polypeptide chain, a terminator ("TER") is indicated. One of skill in the art would be able to deduce an amino acid sequence directly from a PDB file, with no additional information. Accordingly, the PDB files presented in the instant specification provide written description support for each amino acid sequence listed as SEQ ID NO: 52 to SEQ ID NO: 60, and no new matter is introduced by way of the substitute sequence listing.

Drawings

In response to the Examiner's request for an amended drawing (FIG. 7), Applicants submit on even date herewith a request to amend drawings under 37 C.F.R. § 1.121(d) accompanied by a marked up version of FIG. 7 showing the proposed amendment. The Examiner is kindly asked to consider the amended drawing.

Amendments to the Specification

Applicants have amended the specification at paragraphs **[0146]**, **[0158]** and **[0160]**, to include SEQ ID NOs for the sequences of protein fragments presented in the Protein Data Bank (PDB) files found in, respectively, Appendices 1–3 of the specification as filed. The specification at paragraph **[0146]** has additionally been amended to incorporate remarks found in the headers to the PDB files of Appendix 1 (specification as filed, page 74, lines 9-20).

Applicants have also amended the specification to correct a number of minor typographical defects. In particular, the spelling of the word "spatially" has been corrected in paragraphs **[0014]**, **[0017]**, **[0019]**, **[0044]**, **[0045]**, and **[0046]**. The spelling of the word "interactive" has been corrected in paragraph **[0071]**. Additionally, the amino acid residue denoted "V284" has been written out in full, according to standard 3-letter amino acid abbreviations, as "Val 284" in paragraph **[0044]**. No new matter has been introduced by way of these amendments and entry thereof is respectfully requested.

Amendments to the Claims

Claims 1, 3-5, 12 and 15 have been amended to correct a number of informalities. Specifically, claim 1 is amended to introduce the conjunction "thereby" before the last step.

Claim 3 has been amended to correct the recitation of amino acid residue "Val284". The Examiner is thanked for pointing out this typographical error which appeared in the copy of pending claims presented in Appendix C of Applicants' amendment and response, mailed April 25, 2002. Applicants take this opportunity to point out that the error in question was merely a typographical error and did not appear in Appendix B, nor in the body of the amendment and response, mailed April 25, 2002. Applicants apologize for causing the Examiner the inconvenience associated with issuing a § 112 objection in respect of this matter.

Applicants have also amended claims 3-5 to correct typographical errors in the presentation of isoleucine residues, Ile280 and Ile302, and glutamine residue Glu457. Specifically, in each case the "l" of "Ile" or "Glu" had been presented as the numeral "1".

Applicants have amended claim 12 to correct the indefinite article, as pointed out by the examiner, and claim 15 to insert an indefinite article before "peptidomimetic".

Applicants have further amended claims 2 – 8 to introduce SEQ ID NO: 52 or SEQ ID NO: 53, which refer to a protein fragment described in the PDB file presented in Appendix 1 of the specification as filed. As discussed hereinbelow, this amendment has been introduced to more particularly point out the protein sequence referred to in the claims.

Finally, with this amendment, Applicants have introduced new claims 32 to 43. Support for claims 32 and 33 is found in paragraph **[0012]** of the specification as filed. Claims 34 and 35 are supported by the crystal structures found in Appendices 2 and 3 of the specification as filed, as well as the alignments found in FIG. 19. Claims 36–43 are supported by the alignments found in FIG. 19 of the specification as filed.

No new matter is added by the amendment of Claims 1-8, 12 and 15, and the addition of new Claims 32 to 43. Accordingly, entry into the instant Application is proper and respectfully requested.

Objections to the claims

As discussed hereinabove, Applicants have amended claims 3 and 12 to take account of the typographical errors pointed out by the Examiner.

Rejections under 35 U.S.C. § 112 (¶ 2)

Claim 2–9 stand rejected under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner has pointed out the existence of at least two different human thyroid receptors, designated alpha and beta, with different respective sequences and sequence numberings. As a result, the Examiner has stated that Applicant's claims, in which "residues of human thyroid receptor" have been identified, do not permit one of skill in the art to ascertain which residues must be used for homology alignment.

Applicants have reviewed the sequences whose NCBI accession numbers were identified by the Examiner, and concur in the numbering that she has pointed out. Nevertheless, Applicants believe that one of skill in the art would appreciate that the residue labeling employed in Applicants' specification referred to the protein fragments presented in the PDB file of Appendix 1 of the specification as filed. Accordingly, Applicants' amendments, herein, have attached a SEQ ID NO to each protein fragment in Appendix 1 of the specification as filed, and have amended claims 2–9 to refer explicitly to a SEQ ID NO of a protein fragment in Appendix 1, as well as to specify that such sequences are to be found in a human thyroid *beta* receptor.

In view of the foregoing, Applicants respectfully request that the rejection of claims 2–9 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 102 (e)

Claims 1–10, 12-15, 30 and 31 stand rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by U.S. Patent no. 6,266,622, to Scanlan *et al.*, (hereinafter "Scanlan"). Applicants respectfully traverse the rejection.

Anticipation of a claim requires that the reference teach every element of the claim. MPEP § 2131. Applicants acknowledge that the technical matters that are germane to the present invention are of some considerable subtlety and are concerned that, hitherto, Applicants have perhaps not articulated them to the Examiner with requisite precision. Hence, Applicants take this opportunity to explain in further detail the differences between the teachings of the cited references and the claimed invention.

Applicants' claimed invention is a "method of identifying a compound that *binds to a coactivator binding site* of a nuclear receptor," comprising modeling and screening steps. Applicants have discovered the location and identity of the coactivator binding site (specification as filed, ¶ **[0041]**). Specifically, the coactivator binding site is a "small cluster of residues on the *surface* of the LBD ['ligand binding domain'] that form a prominent hydrophobic cleft." (specification as filed, ¶ **[0041]**). Thus, the coactivator binding site is a specific part of the LBD that has its own binding characteristics. Furthermore, Applicants have identified amino acid residues that define the coactivator binding site, and have shown how to design a molecule that will selectively bind to such residues.

In general, function of nuclear receptors utilizes both a hormone, which binds to a ligand binding pocket in the interior of the LBD, and a coactivator (or corepressor) that binds to the coactivator binding site on the surface of the LBD. The ligand binding pocket is distinct from the coactivator binding site in that the former is in the interior of the LBD whereas the latter is on the surface. This capacity for dual binding gives rise to a number of different ways of modulating receptor activity. Applicants teach a method that comprises binding a molecule to the coactivator binding site, independently of a hormone or other ligand that may also bind to the LBD. Thus, by producing molecules that bind the coactivator binding site, overall receptor function may be modulated because the overall function depends upon both the hormone and a particular coactivator.

By contrast, Scanlan does not teach the structure of the coactivator binding site. The Examiner has pointed to a teaching at Col.24 of Scanlan as suggesting that Scanlan teaches methods of identifying molecules that block or promote coactivator binding. However, although Scanlan admits the existence of the coactivator binding site it does not delineate with specificity the residues of which it is comprised. In particular, Scanlan acknowledges that the coactivator binding site is only "approximately" known, and refers only to residues 1005-1022 (Scanlan, Col.13, lines 38-39). By contrast, as demonstrated in Applicants' instant specification, the coactivator binding site comprises many more residues than those suggested by Scanlan. In particular, it is Applicants' *discovery* that the coactivator binding site comprises residues from helices 3, 4, 5, 6 and 12 (paragraph **[0041]**) that enabled them to articulate methods of designing molecules that would bind directly to the coactivator binding site. Accordingly, because Scanlan does not teach the constituent residues of the coactivator

binding site, one of ordinary skill in the art would not have been able to design molecules that bind to the coactivator binding site upon reading Scanlan.

Additionally, the Examiner has asserted that "Scanlon [sic] specifically teaches fitting of compounds to TR-beta wherein the atomic structural model of TR-beta comprises coordinates for amino acids Ile280, Thr281, ... Phe459 (Appendices 7 and 8), thereby anticipating claims 2-8." However, Applicant respectfully submits that in order for Scanlan to anticipate Applicants' claimed invention, it must teach the coactivator binding site with specificity. The mere recitation of the residues by the Examiner, and their mere presence in the appendices of Scanlan, is not sufficient to identify the coactivator binding site itself with precision.

Furthermore, the only method envisaged by Scanlan for affecting coactivator binding is indirect. As discussed by Scanlan, upon binding of a ligand to a ligand binding pocket in the interior of the LBD, the receptor undergoes a conformational change that facilitates accommodation of a coactivator or corepressor (Scanlan, Col. 14, lines 1-21). Scanlan then teaches that a computationally designed ligand could be found that alters activation of coactivators (or corepressors) with the receptor (Scanlan, Col. 14, lines 33-53). In other words, one of skill in the art, reading Scanlan, would appreciate that Scanlan is not teaching a method of identifying a ligand that *binds* to the coactivator binding site, but instead is teaching a ligand that binds to a ligand binding pocket inside the LBD as a result of which coactivator binding may also be simultaneously disrupted.

The description in Scanlan at Col. 14, lines 30-33 signals one way in which coactivator binding may be disrupted *viz.*: by designing "ligands that contain an extension moiety that coordinates the activation domain of the nuclear receptor". This interpretation is further borne out by the teaching at Cols. 24-25 of Scanlan. This section was interpreted by the Examiner to be a teaching that "[Scanlan]'s antagonists or agonists can block or promote binding of a coactivator." However, the mechanism by which such blocking or promoting is accomplished is not through a direct binding of a molecule to the *coactivator* binding site. Instead blocking or promoting is achieved by binding a ligand to the ligand binding pocket and through use of an "extended chemical moiety from the *ligand* that disrupts the binding or contact of the activation domain with co-activator and/or co-repressor." (Scanlan, Col. 24, lines 49-52; emphasis added.) In other words, Scanlan contemplates a single molecule that,

although binding to the interior of the LBD, is able to simultaneously affect coactivator binding through a steric type of interaction. (See also, Scanlan, Col. 25, lines 6-9; Col. 28, line 55 - Col. 29, line 27, in particular Col. 27, lines 25-27: "[s]uch protruding extensions could present a *steric blockade* to interactions with co-activators or other proteins." (emphasis added).) Indeed, exemplary compounds suggested by Scanlan, and shown in Scanlan, FIG. 10, have an "extension group" that could clearly provide the envisaged "steric blockade" if suitably positioned.

Accordingly, Scanlan does not teach or suggest each and every limitation of Claim 1. In particular, Scanlan does not teach the structure of the coactivator binding site and does not teach methods of identifying ligands that bind directly to the coactivator binding site. Claims 2-10, 12-15 and 30 depend, either directly or indirectly, from independent Claim 1 and are thus patentable for at least the same reason. In view of the foregoing, Applicants respectfully request that the rejection of Claims 1-10, 12-15, 30 and 31 under 35 U.S.C. § 102 (b) over Scanlan be withdrawn.

Rejections under 35 U.S.C. § 103 (a)

Rejection over Scanlan in view of Kuntz

Claims 1-15, and 30-31 stand rejected under 35 U.S.C. § 103 (a) as being allegedly obvious over Scanlan in view of Kuntz *et al.*, *Science*, 257, 1078–1082, (1992) (hereinafter "Kuntz"). Applicants respectfully traverse the rejection because the Examiner has not made out a *prima facie* case.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, a basic criterion that must be met is that the prior art reference or references, when combined, must teach or suggest each and every limitation of the claimed invention. M.P.E.P. § 706.02(j). If this criterion is not met, *prima facie* obviousness is not established.

As discussed hereinabove, Scanlan does not teach or suggest every limitation of the invention recited in amended Claim 1 because Scanlan does not teach identifying ligands that bind to the coactivator binding site of a nuclear receptor. Kuntz does not provide the missing teachings. As indicated by the Examiner, Kuntz teaches high throughput screening in

conjunction with structure-based design. Kuntz says nothing whatsoever about coactivator binding sites of nuclear receptors. Accordingly, Kuntz fails to cure the deficiency of Scanlan to provide the invention recited in Claim 1.

Claims 2-10, 12, 14, 15 and 30 depend either directly or indirectly from independent Claim 1 and are thus patentable for at least the same reasons as Claim 1. In view of the foregoing, Applicants respectfully request that the rejection of Claims 1-15, and 30-31 under 35 U.S.C. § 103 (a) over Scanlan in view of Kuntz be withdrawn.

Rejection over Scanlan in view of Heery

Claims 1 – 10, 12 – 16, and 30 – 31 stand rejected under 35 U.S.C. § 103 (a) as being allegedly obvious over Scanlan in view of Heery *et al.*, *Nature*, 387, 733–736, (1997) (hereinafter "Heery"). Applicants respectfully traverse the rejection because the Examiner has not made out a *prima facie* case. As discussed hereinabove, to establish a *prima facie* case, the burden is on the Examiner to show that the prior art reference or references, when combined, teach or suggest each and every limitation of the claimed invention.

Applicants' claimed invention comprises "using an atomic structural model of the nuclear receptor coactivator binding site or portion thereof." Heery does not provide such a model.

The Examiner has asserted that "Scanlon [sic] teaches a method of identifying compounds which bind to a ligand binding site on a thyroid receptor and alter the activity of the receptor (*e.g.*, a coactivator)" and that "Heery teaches motifs comprising an LxxLL sequence which are necessary and sufficient for binding of coactivators to ligand binding domains of nuclear receptors." As discussed hereinabove, Scanlan does not teach identifying compounds that bind to the *coactivator* binding site on the surface of the ligand binding domain. Moreover, as also discussed hereinabove, Scanlan does not identify the constituent residues of the coactivator binding site. The deficiencies of Scanlan are not provided by Heery.

Heery identifies a sequence motif (denoted "LXXLL") that is proposed to be a signature sequence for facilitating the interaction of different proteins with nuclear receptors. However, mere identification of such a sequence does not identify the coactivator binding site with any specificity. Using the familiar "lock and key" model of drug interaction as an

analogy, Heery has taught a feature of a key that fits into the lock in question (the coactivator binding site). Knowing the key alone is not sufficient to deduce the structure of the lock. Thus Heery's teaching of a sequence that binds to the coactivator binding site does not provide one of skill in the art missing information about the structure of the coactivator binding site itself.

Nor does Heery provide an atomic structural model of the coactivator binding site that would permit one of ordinary skill in the art to identify other molecules that would bind to it. In practical terms, Heery is attempting to accomplish empirically what Applicant is able to do, but without the advantage of knowing the structure of the coactivator binding site. Merely knowing a feature of proteins that bind to a binding site is not enough, by itself, to *model* "test compounds that fit spatially into the nuclear receptor coactivator binding site" as required by Applicants' claims.

Dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." *In re Fine,* 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03. Claims 2 – 10, 12 – 16, 30 and 31 depend either directly or indirectly from independent Claim 1 and are thus patentable for at least the same reasons as Claim 1. In view of the foregoing, Applicants respectfully request that the rejection of Claims 1, 10, 11-13, and 30 under 35 U.S.C. § 103 (a) over Scanlan in view of Heery be withdrawn.

In summary, in light of Applicant's remarks hereinabove, in response to the rejection of Claim 1, which show that the combined teachings of Scanlan and Kuntz or Heery fail to recite each and every limitation of Applicant's claimed invention, Applicant respectfully requests that the rejection of Claims 1 – 10, 12 – 16, 30 and 31 be withdrawn.

CONCLUSION

Applicants respectfully submit that all pending Claims of the instant Application satisfy all requirements for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested.

No other fees are believed due in connection with this Amendment. However, the Commissioner is authorized to charge any required fee not included with this Amendment or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150 (9811-008-999). A duplicate copy of this sheet is enclosed for such purpose.

If the Examiner determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (212) 790-6578.

Respectfully submitted,

Date November 18, 2002

Richard G. A. Bone
(Limited recognition under 37 C.F.R. § 10.9(b);
copy of certificate attached hereto.)

for Samuel B. Abrams (Reg. No. 30,605)
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Enclosure

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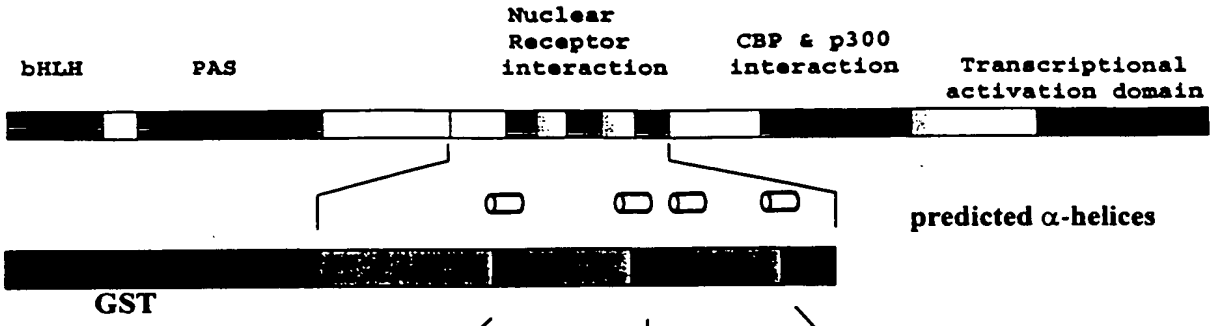
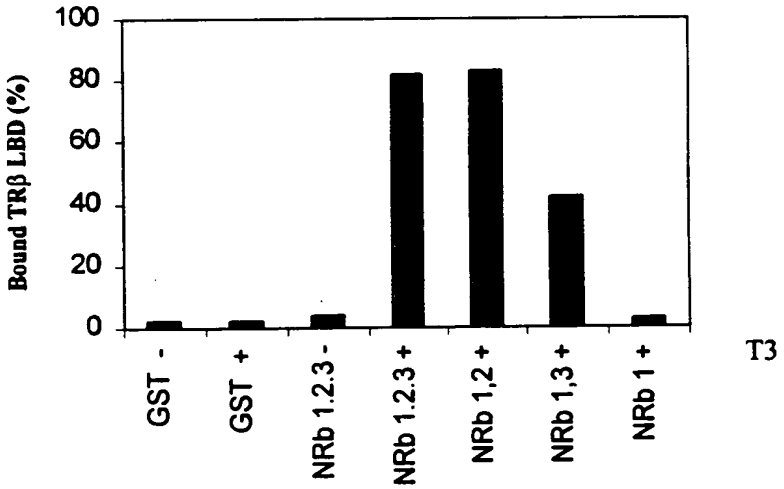
FIGURE 7



	NR-box1 residues 15-21 SEQ ID NO: 5	~~NR-box1~~ NR-box2 residues 15-21 SEQ ID NO: 6	NR box3 residues 15-21 SEQ ID NO: 7
NRb 1,2,3	KLLQLLT.	.ILHRLLQ.	.LLRYLLD
NRb 1,2	KLLQLLT.	.ILHRLLQ.	.AARAAAD
NRb 1,3	KLLQLLT.	.AAHRAAQ.	.LLRYLLD
NRb 1	KLLQLLT.	.AAHRAAQ.	.AARAAAD



APPENDIX A:
CHANGES TO SPECIFICATION
UPON ENTRY OF THE AMENDMENT FILED November 18, 2002

U.S. PATENT APPLICATION SERIAL No. 09/281,717
(ATTORNEY DOCKET NO. 9811-008-999)

The following mark-up scheme is adopted:
Deleted material: ~~Strike-through~~;
Inserted material: **Bold Underline**.

Please amend paragraph **[0014]** *as follows*:

[0014] The present invention further provides methods for identifying and designing small molecules that bind to the coactivator binding site using atomic models of nuclear receptors. The method involves modeling test compounds that fit ~~spacially~~ **spatially** into a nuclear receptor coactivator binding site of interest using an atomic structural model comprising a nuclear receptor coactivator binding site or portion thereof, screening the test compounds in a biological assay characterized by binding of a test compound to a nuclear receptor coactivator binding site, and identifying a test compound that modulates coactivator binding to the nuclear receptor.

Please amend paragraph **[0017]** *as follows*:

[0017] The invention further includes a method for identifying an agonist or antagonist of coactivator binding to a nuclear receptor. The method comprises providing the atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system; modeling compounds which fit ~~spacially~~ **spatially** into the nuclear receptor coactivator binding site; and identifying in an assay for nuclear receptor activity a compound that increases or decreases activity of the nuclear receptor through binding the coactivator binding site.

Please amend paragraph **[0019]** *as follows*:

[0019] Also provided is a method of identifying a compound that selectively modulates the activity of one type of nuclear receptor compared to other nuclear receptors. The method is exemplified by modeling test compounds that fit ~~spacially~~ **spatially** and preferentially into a nuclear receptor coactivator binding site of interest using an atomic structural model of a

nuclear receptor coactivator binding site, selecting a compound that interacts with one or more residues of the coactivator binding site unique in the context of that site, and identifying in an assay for coactivator binding activity a compound that selectively binds to the coactivator binding site compared to other nuclear receptors. The unique features involved in receptor-selective coactivator binding can be identified by comparing atomic models of different receptors or isoforms of the same type of receptor.

Please amend paragraph **[0044]** *as follows*:

[0044] Compounds that bind to the coactivator binding site of nuclear receptors can be identified by computational modeling and/or screening. For example, coactivator agonists or antagonists can be identified by providing atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system, modeling them, and identifying compounds that fit ~~spacially~~ **spatially** into the coactivator binding site. By a "portion thereof" is intended the atomic coordinates corresponding to a sufficient number of residues or their atoms of the coactivator binding site that interact with a compound capable of binding to the site. This includes receptor residues having an atom within 4.5Å of a bound compound or fragment thereof. For instance, human TR residues ~~V284~~ **Val284**, Phe293, Ile302, Leu305 and Leu454 contain side chain atoms that are within 4.5Å, and interact with, hydrophobic residues of a (SEQ ID NO: 1) LxxLL motif of an NR-box 2 coactivator peptide. As another example, an atomic structural model utilized for computational modeling and/or screening of compounds that bind to the coactivator binding site may include a portion of atomic coordinates of amino acid residues corresponding to the site composed of residues of human thyroid receptor selected from Val284, Lys288, Ile302, Lys306, Leu454 and Glu457, or their structural and functional equivalents found in other receptors. Thus, for example, the atomic coordinates provided to the modeling system can contain atoms of the nuclear receptor LBD, part of the LBD such as atoms corresponding to the coactivator binding site or a subset of atoms useful in the modeling and design of compounds that bind to a coactivator binding site.

Please amend paragraph **[0045]** *as follows*:

[0045] The atomic coordinates of a compound that fits into the coactivator binding site also can be used for modeling to identify compounds or fragments that bind the site. By "modeling" is intended quantitative and qualitative analysis of molecular structure/function based on atomic structural information and receptor-coactivator agonists/antagonists interaction models. This includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models. Modeling is preferably performed using a computer and may be further optimized using known methods. By "fits ~~spacially~~ **spatially**" is intended that the three-dimensional structure of a compound is accommodated geometrically by a cavity or pocket of a nuclear receptor coactivator binding site.

Please amend paragraph **[0046]** *as follows*:

[0046] Compounds of particular interest fit ~~spacially~~ **spatially** and preferentially into the coactivator binding site. By "fits ~~spacially~~ **spatially** and preferentially" is intended that a compound possesses a three-dimensional structure and conformation for selectively interacting with a nuclear receptor coactivator binding site. Compounds that fit ~~spacially~~ **spatially** and preferentially into the coactivator binding site interact with amino acid residues forming the hydrophobic cleft of this site. In particular, the hydrophobic cleft of the coactivator binding site comprises a small cluster of hydrophobic residues. The site also contains polar or charged residues at its periphery. The present invention also includes a method for identifying a compound capable of selectively modulating coactivator binding to different nuclear receptors. The method comprises the steps of modeling test compounds that fit ~~spacially~~ **spatially** and preferentially into the coactivator binding site of a nuclear receptor of interest using an atomic structural model of a nuclear receptor, screening the test compounds in a biological assay for nuclear receptor activity characterized by preferential binding of a test compound to the coactivator binding site of a nuclear receptor, and identifying a test compound that selectively modulates the activity of a nuclear receptor. Such receptor-specific compounds are selected that exploit differences between the coactivator binding sites of one type of receptor versus a second type of receptor, such as the differences depicted in **Figure 19**.

Please amend paragraph **[0071]** *as follows*:

[0071] The machine-readable data storage medium can be used for ~~interative~~ **interactive** drug design and molecular replacement studies. For example, a data storage material is encoded with a first set of machine-readable data that can be combined with a second set of machine-readable data. For molecular replacement, the first set of data can comprise a Fourier transform of at least a portion of the structural coordinates of the nuclear receptor or portion thereof of interest, and the second data set comprises an X-ray diffraction pattern of the molecule or molecular complex of interest. Using a machine programmed with instructions for using the first and second data sets a portion or all of the structure coordinates corresponding to the second data can be determined.

Please amend paragraph **[0146]** *as follows*:

Several peptides containing GRIP1 NR-box 2 were tested in crystallization trials with the hTRβ LBD. The complex of the hTRβ LBD with the GRIP1 NR-box 2 peptide 686-KHKILHRLLQDSS-698 (residues 12-24 of SEQ ID NO: 6) produced crystals that were dependent on both the presence and the concentration of the peptide. Without the peptide, the hTRβ LBD precipitated immediately. However, nucleation was erratic, but could be overcome through seeding of prepared drops with microcrystals of the hTRβ LBD:GRIP1 NR-box 2 peptide complex. Structure of the hTRβ LBD:GRIP1 NR-box 2 peptide complex was determined by molecular replacement using the structure of the hTRβ LBD determined previously (Wagner *et al.*, *supra*) and refined to a resolution of 3.6Å (Table 1). The refined model consists of residues K211-P254 and V264-D461 of monomer 1 of the hTRβ LBD, residues K211-P254 and G261-D461 of monomer 2 of the hTRβ LBD, and the GRIP1 NR-box 2 peptides (residues 14-24 of SEQ ID NO: 6) 688-KILHRLLQDSS-698, and (residues 14-22 of SEQ ID NO: 6) 688-KILHRLLQD-696 (Appendix 1). **The structure in Appendix 1 consists of: a portion of each of two molecules of hTRβ, chain A (SEQ ID NO: 52) and chain B (SEQ ID NO: 53); two molecules of T_3, chain J and chain K; and two molecules of GRIP-1 peptide, chain X (SEQ ID NO: 54) and chain Y (SEQ ID NO: 55)**.

Please amend paragraph **[0158]** *as follows*:

Ile 689 from the peptide interacts with three receptor residues (Asp 538, Glu 542 and Leu 539). The γ-carboxylate of Glu 542 forms hydrogen bonds to the amides of residues 689 and 690 of the peptide. A water-mediated hydrogen bond network is formed between the imidazole ring of His 377, the γ-carboxylate of Glu 380, and the amide of Tyr 537. Three residues (Glu 380, Leu 536 and Tyr 537) interact with each other through van der Waals contacts and/or hydrogen bonds. Intriguingly, mutations in each these three residues dramatically increase the transcription activity of unliganded ERα LBD (Eng, *et al.*, *Mol. Cell. Biol.* (1997) 17:4644-4653); Lazennec, et al., *Mol Endocrinol.* (1997) 11:1375-86; White, *et al.*, *EMBO J.* (1997) 16:1427-35). Atomic coordinates of DES-LBD-peptide complex are attached as Appendix 2. **The structure in Appendix 2 consists of: a portion of human ERα, chain A (SEQ ID NO: 56) and chain B (SEQ ID NO: 57); two molecules of DES; and two molecules of GRIP-1 NR-box 2 peptide, chain C (SEQ ID NO: 58) and chain D (SEQ ID NO: 59)**.

Please amend paragraph **[0160]** *as follows*:

The OHT complex data set was then collected. Starting with one of the monomers of the preliminary low-resolution DES-hERα LBD-NR-box 2 peptide model as the search probe, molecular replacement in AMoRe was used to search for the location of LBD in this crystal form in both $P6_122$ and $P6_522$. A translation search in $P6_522$ yielded the correct solution (R=53.8%, CC=38.2%). In order to reduce model bias, DMMULTI (CCP4, 1994) was then used to project averaged density from the DES complex cell into the OHT complex cell. Using MOLOC, a model of the hERα LBD was built into the resulting density. The model was refined initially in REFMAC and later with the simulated annealing, positional and R-factor refinement protocols in X-PLOR (Brunger, X-PLOR. Version 3.843, New Haven, Connecticut: Yale University, 1996) using a maximum-likelihood target (Adams, *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94:5018-23). Anisotropic scaling and a bulk solvent correction were used and all B-factors were refined isotropically. Except for the R_{free} set (a random sampling consisting of 8% of the data set), all data between 41 and 1.9 Å (with no σ cutoff) were included. The final model consisted of residues 306-551, the ligand and 78 waters. According to PROCHECK (CCP4, 1994), 91.6% of all residues in the model were in the core

regions of the Ramachandran plot and none were in the disallowed regions. Thus, the structure of the OHT-hERα LBD complex has been refined against data of comparable resolution (1.90 Å) to a crystallographic B-factor of 23.0% (R_{free} =26.2%). Atomic coordinates of OHT-hERα LBD complex are attached as Appendix 3. **The structure in Appendix 3 consists of: atomic coordinates for a portion of human ERα,(SEQ ID NO: 60) complexed with OHT**.

APPENDIX B

CHANGES TO CLAIMS
UPON ENTRY OF THE AMENDMENT MAILED November 18, 2002

U.S. PATENT APPLICATION SERIAL NO. 09/281,717
(ATTORNEY DOCKET NO. 9811-008-999)

The following mark-up scheme is adopted:
Deleted material: ~~Strike-through~~;
Inserted material: **Bold Underline**.

1. (Amended three times) A method of identifying a compound that binds to a coactivator binding site of a nuclear receptor, said method comprising:

modeling test compounds that fit spatially into the nuclear receptor coactivator binding site using an atomic structural model of the nuclear receptor coactivator binding site or portion thereof~~,~~**; and**

screening said test compounds in an assay that measures binding of a test compound to the nuclear receptor coactivator binding site, ~~and~~ **thereby**

identifying a test compound that binds to the coactivator binding site of said nuclear receptor.

2. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with residues of **a portion of** human thyroid **beta** receptor **(SEQ ID NO: 52 or SEQ ID NO:53)** selected from the group consisting of Val284, Phe293, Ile302, Leu305, and Leu454.

3. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with residues of **a portion of** human thyroid **beta** receptor **(SEQ ID NO: 52 or SEQ ID NO:53)** selected from the group consisting of ~~Val84~~ **Val284**, Lys288, ~~Ile302~~ **Ile302**, Lys306, Leu454 and ~~Glu457~~ **Glu457**.

4. (Amended twice) The method of claim 1, wherein said atomic structural model comprises atomic coordinates of amino acid residues identified by homology alignment with ~~residues of human thyroid receptor~~ helix 3 residues ~~Hc280~~ **Ile280**, Thr281, Val283, Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln30l, Ile302, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, ~~G1u457~~ **Glu457**, Val458 and Phe459 **found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53)**.

5. (Amended twice) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with residues ~~of human thyroid receptor~~ selected from the group consisting of helix 3 residues ~~Hc280~~ **Ile280**, Thr281, Val283, Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln301, ~~Hc302~~ **Ile302**, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, Glu457, Val458 and Phe459 **found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53)**.

6. (Amended twice) The method of claim 5, wherein said amino acid residues identified by homology alignment with residues of **a portion of** human thyroid **beta** receptor **(SEQ ID NO: 52 or SEQ ID NO:53)** comprise Val284, Phe293, I1e302, Leu305, and Leu454.

7. (Amended twice) The method of claim 5, wherein said amino acid residues identified by homology alignment with residues of **a portion of** human thyroid **beta** receptor **(SEQ ID NO: 52 or SEQ ID NO:53)** comprise Val284, Lys288, I1e302, Lys306, Leu454 and G1u457.

8. (Amended twice) The method of claim 1, wherein said nuclear receptor coactivator binding site comprises amino acid residues identified by homology alignment with ~~residues of human thyroid receptor of~~ helix 3 residues Ile280, Thr281, Val283, Val284, Ala287, and Lys288, helix 4 residue Phe293, helix 5 residues Gln30l, Ile302, Leu305, Lys306, helix 6 residue Cys309, and helix 12 residues Pro453, Leu454, G1u457, Val458 and

Phe459 **found in a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO:53)**.

12. (Amended twice) The method of claim 1, wherein said assay is ~~a~~ **an** *in vivo* assay.

15. (Amended) The method of claim 14, wherein said test compound is a small organic molecule, a peptide, or **a** peptidomimetic.